1. BENEFITS OF ACCUTANE

1.1 Etiology and Pathology of Acne

- ***Acne is a common disease that effects the population from early adolescents through adulthood.***
- ***If untreated, acne can lead to physical scarring with associated psychological effects.***

Acne is the most common disease treated by dermatologists based upon data from the 1996 U.S. Census. The lifetime prevalence of acne approaches 90%. Acne vulgaris is a chronic disease with the highest prevalence in adolescents. The onset of acne vulgaris occurs during the onset of puberty, which is at a younger chronological age in females than in males. Both females and males have acne that extends into adulthood, with females often having a higher prevalence of the disease as well as more severe forms during adulthood. When untreated, acne usually lasts for several years until it spontaneously remits [Strauss and Thiboutot, 1999]. Most cases continue into the mid-twenties, and there is evidence that the duration of acne may last into middle age for most women [Goulden et al., 1999].

The etiology of acne is multi-factorial. The pathogenesis stems primarily from four endogenous factors: increased sebum production, hypercornification of the infundibulum of the pilosebaceous gland, increased proliferation of microbial flora, and subsequent inflammatory responses. At puberty, increased androgen production causes an increase in the size and activity of the pilosebaceous gland. The disease begins as a pathological condition involving a microcomedo and progresses from hypercornification of the infundibulum of the pilosebaceous gland to blockage and eventual formation of a comedo composed of sebum, keratin, and the bacteria *Propionibacterium acnes* [Strauss and Thiboutot, 1999]. Follicular eruption releases sebum breakdown products that irritate the follicular wall and induce an inflammatory reaction. The response of individual patients to different treatments varies due to the different endogenous factors and complex etiology of the disease.

Inflammatory acne is characterized by the presence of the following types of lesions: papules, pustules, cysts, and nodules. The presence of cysts and nodules characterizes the severe type of acne designated “cystic acne” or “nodular acne”; the two terms are typically used interchangeably. While acne can be graded on the type, number and distribution of lesions, there is no generally accepted method for characterizing acne severity or type.

Large numbers of inflammatory papules, pustules, nodules and cysts are common features of severe cystic acne. These nodular lesions may be deeply inflamed, palpable and often painful. Moreover, they can be very large, often more than ten millimeters across and may coalesce or overlap. The nodules of severe acne are located primarily on the face, neck, chest and back. When left untreated, the classic pitted “acne scars” or flat, macular scarring invariably accompany this type of acne. A severe variant of acne, acne conglobata, is characterized by secondary infections with sinus tract infections and disfiguring scars with involvement of most parts of the face including the scalp and much of the trunk.

In addition to long-term physical disfigurement, substantial psychological disruption accompanies acne, especially in adolescents and young adults. Acne has been shown to increase symptoms of anxiety and depression, to lower self-esteem [Rubinow et al., 1987; Gupta et al., 1998], and to produce social impairment or even anger [Koo, 1995]. Acne is perceived by adolescents as having negative personal and social consequences [Krowchuk, 1991]. Indeed, no disease has caused more insecurity and feelings of inferiority than acne [Koo, 1995]. The best treatment for patients with this prognosis is an aggressive regimen initiated as early as possible to prevent physical and psychological scarring.

1.2 Acne Treatments

- ***Efficacious treatments exist for most types of acne.***
- ***The risk-benefit of each potential treatment regimen must be carefully considered.***
- ***Severe cystic acne should be shown to be recalcitrant to other therapies before treatment with Accutane is initiated.***

Acne is currently being treated with a variety of agents including antibiotics (particularly broad-spectrum antibiotics), antibacterial agents, hormones, and retinoids. Topical acne treatments include such drugs as benzoyl peroxide, tretinoin, azeleic acid, clindamycin, erythromycin, adapalene and tazarotene. Oral acne therapies include drugs such as benzamycin, tetracycline, minocycline, and isotretinoin.

1.2.1 Topical therapies

Topical therapies are most efficacious for the milder and moderate forms of acne, and are often used in combination with systemic antibiotic or hormonal therapies. Most of the topicals are bacteriostatic and comedolytic agents; some, though, also contain retinoids and so cannot be used in conjunction with Accutane.

Topical retinoids may act by effecting the keratinization of the follicular canals and thus allowing the sebum to be expressed and not impact in the sebaceous gland follicles. Some reduction of sebum excretion is likely as well. Irritation from topical treatments is observed in many patients that use them for extended periods or at higher concentrations. Previously, high dose estrogen therapy (over 75 micrograms) was used routinely for treatment of severe acne in women. However the risk of vascular and thrombic side effects requires that this therapy be used only when absolutely necessary.

Recently, a combination contraceptive pill with lower doses of estrogen and a progestin component, Ortho Tricyclen, was approved for use in patients with acne vulgaris. The efficacy results presented in the Ortho Tricyclen package insert were from two clinical trials in acne which was not recalcitrant nodular/cystic that showed a 56% reduction in inflammatory lesions compared to a 36% reduction in the placebo control groups. Estrogen/progestin-containing oral contraceptives such as Ortho Tricyclen can cause side effects such as nausea, weight gain, spotting, breast tenderness, amenorrhea, and melasma. The effectiveness of the oral contraceptives for reduction of cysts and nodules in severe acne has not been demonstrated in clinical trials and their use is limited to patients with small numbers of these inflammatory

lesions. However the use of oral contraceptives for the treatment of acne is increasing. This may have added benefit for women who eventually obtain Accutane therapy since they will have already been initiated with one of the two forms of effective contraception that needs to be used.

1.2.2 Antibiotics

Among systemic antibiotics, the original tetracyclines, doxycyclines and erythromycins, as well as some of the newer generation, such as the minocyclins, are efficacious. Sulphanilamide drugs such as cotrimoxazole are often used in patients who should not use, or are resistant to, the tetracyclines or erthryomycins.

The efficacy of broad-spectrum antibiotics used to treat severe acne may result primarily from their ability to decrease free fatty acid concentrations [Freinkel et al., 1965]. This decrease may occur directly through suppression of the number of *P. acnes*, and secondarily through anti-inflammatory activity, reduces proinflammatory by-products of bacterial infections in the acne lesions. It may take several weeks for these reductions to become evident. Individual lesions may require several weeks to undergo resolution of the acne condition. While the decrease in free fatty acids observed strengthens the rationale for tetracycline use, these compounds have an affinity for rapidly mineralizing tissues (i.e. growing fetal bone) and are contraindicated in pregnancy or growing children. Decreases in free fatty acid formation have also been reported with erythromycin, demethylchlortetracycline, clindamycin, and minocycline. Doxycycline and minocycline appear to be more effective than tetracycline. The major disadvantage of the use of doxycycline is that it produces photosensitivity reactions, and patients should be switched to another antibiotic, if possible, during the summer months. Patients on minocycline should be monitored carefully as the drug can cause blue-black pigmentation, especially in the scars as well as elsewhere [Layton and Cunliffe, 1989].

Patients receiving common antibiotics are often on these medications for extended periods of time. As Eady [1998] has pointed out, antibiotic therapy for acne promotes resistance within the cutaneous population of *P. acnes*. Patients who are poor responders or who have been treated for extended period of time with antibiotics are likely to carry antibiotic resistant bacteria [Eady, 1998]. The recommendations to prevent the spread of antibiotic resistance strains include treating patients for as short as time as possible with antibiotics: 6 months for oral antibiotics and 3 months for topical antibiotics [Eady, 1998]. This recommendation has been adopted by some managed care treatment guidelines for severe acne.

In direct comparisons of antibiotics with Accutane, reductions in the number and size of cysts were always significantly greater with Accutane therapy and remained so during follow-up. A small study comparing Accutane with tetracycline treatment showed that Accutane produced greater reductions in the number and size of cysts at all timepoints [Lester et al., 1985]. Similarly, a head-to-head comparison of Accutane and minocycline showed an even wider separation of effect on the number and size of cysts with differences evident even as early as 2-4 weeks of therapy [Pigatto et al., 1986].

The antibiotics are an efficacious therapy for the treatment of acne in that they reduce the effect of the inflammation associated with severe forms of acne. However, since the mechanism of action of these medications does not mitigate the underlying etiology of the disease many patients

either need to remain on therapy for extended periods of time or continue to have cysts and nodules that will likely lead to scarring. In these patients, particularly those with severe acne, the remission of the acne may not occur unless additional therapy is initiated.

1.2.3 Accutane Therapy

As the current label states, Accutane is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition, means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, Accutane should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics." In addition, for female patients of childbearing potential, Accutane is indicated only for those females who are not pregnant. See Appendix 1 for the package insert.

Since 1982 Accutane (isotretinoin, 13-*cis*-retinoic acid) has been available as an effective treatment for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. A single course of therapy has been shown to result in complete and prolonged remission of the disease in the majority of patients. Accutane is currently prescribed at 0.5 to 2 mg/kg given in two divided doses daily with food for 15 to 20 weeks. As indicated in the package insert, the recommended doses are to be administered with food since studies indicate that this increases the bioavailability of the drug. The use of isotretinoin has dramatically changed the management of severe treatment-resistant acne [Chen et al., 1996]. Some improvement is typically seen for 1 to 2 months after isotretinoin is discontinued. Thus, total clearing is not a necessary endpoint for determining when to discontinue isotretinoin therapy. The completeness of the remission in almost all cases and the longevity of the remission, which lasts for months to years in the great majority of patients, are notable characteristics of isotretinoin therapy [Peck et al., 1979; Peck et al., 1982]. Approximately 25% (range 3 – 39%) of patients treated with isotretinoin require a second course of the drug. The likelihood for repeat therapy is increased in younger patients, i.e., those under 16 to 17 years of age. It is recommended to allow at least 2 to 3 months between courses of isotretinoin.

The mechanism of action of isotretinoin is not well understood. The drug produces a rapid and significant inhibition of sebaceous gland activity within 2 to 4 weeks of initiating therapy, and this undoubtedly is of great importance in the initial clearing [Strauss and Stranieri, 1982; Leyden and McGinley, 1982]. In the majority of patients, sebum production returns to normal after 2 to 4 months [Strauss and Stranieri, 1982]. Thus, this action of the drug cannot be used to totally explain the long-term remissions. The *P. acnes* population is also decreased during isotretinoin therapy, which may be due to a decrease in intrafollicular lipids necessary for organism growth [Leyden and McGinley, 1982; Weissman et al., 1981; Leyden et al., 1982; Plewig et al., 1982; Norris et al., 1983]. Isotretinoin also has anti-inflammatory activity as well as an effect on the pattern of follicular keratinization [Plewig et al., 1982].

Accutane is **not** effective for severe acne that manifests itself with multiple macrocomedomes, hormonal dysfunction, or extensive *S. aureus* infections of the skin. Patients with polycystic ovarian syndrome have a hormonal dysfunction that likely does not respond well to Accutane and

may necessitate the need for additional therapy such as cyproterone acetate. Isotretinoin is poorly efficacious for reducing comedomes and thus severe acne patients with predominance of open or closed comedones do not respond well to Accutane therapy.

The use of Accutane requires proper patient selection and patient management for the safe and efficacious use of the drug. The proper patient selection begins the process in which every patient with severe acne needs to be evaluated for their severity and subsequently treated with other therapies in order to attempt to manage the disease, prevent scarring and to assure that failure of other therapies is a precondition for isotretinoin therapy. Once a patient has been shown to not respond to other therapies, the patient needs to be selected based upon their ability to complying with the conditions of Accutane use. Female patients selected for Accutane treatment must avoid pregnancy and must not become pregnant during therapy and for one month following cessation of therapy. The patient must be able to understand and comply with all of the components of the Pregnancy Prevention Program for Women on Accutane (PPP) to prevent fetal exposures to Accutane. In addition, proper monitoring of the Accutane patient requires that laboratory monitoring is indicated for all patients. Because of the frequent side effects and the need for laboratory monitoring and pregnancy evaluation, every patient on Accutane needs to be evaluated at least monthly while on therapy. The proper selection and management of patients for Accutane therapy is indicated in the package insert.

2. ACCUTANE USE AND ACNE PHARMACOEPIDEMIOLOGY

2.1 Overview

This and the following two sections (Sections 3 and 4) delineate the Accutane risk management program with regard to the use of Accutane in women. The safe and effective use of Accutane requires stringent precautions in treating severe recalcitrant nodular acne in women of childbearing potential. To provide context for a discussion of the ways the Pregnancy Prevention Program for Women on Accutane is being enhanced and evaluated on an ongoing basis, this section characterizes the current patterns of acne epidemiology and use of Accutane. This characterization provides a denominator for Accutane use with which to assess pregnancy rates. This approach is one of the components to refine the Pregnancy Prevention Program for Women on Accutane.